EXHIBIT
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Apoptosis and Post-infarction Left Ventricular Remodeling

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[1]*Department of Biochemistry and Biophysics, "E. Cedrangolo", Section of Pathologic Anatomy, Second University of Naples, Naples, Italy,* [2]*Department of Cardiovascular Sciences, University Campus Bio-Medico, Rome, Italy and* [3]*Department of Pathologic Anatomy, University of Trieste, Trieste, Italy*

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A. Baldi, A. Abbate, R. Bussani, G. Patti, R. Melfi, A. Angelini, A. Dobrina, R. Rossiello, F. Silvestri, F. Baldi and G. Di Sciascio. Apoptosis and Post-infarction Left Ventricular Remodeling. *Journal of Molecular and Cellular Cardiology* (2002) 34, 165–174. Apoptosis is a common pathological feature in acute myocardial infarction (AMI), however, its role in the later phases (>10 days) of AMI and in post-infarction left ventricular remodeling has not been characterized. The aim of the study was to identify signs of ongoing cell apoptosis late post AMI. Sixteen hearts were collected at autopsy from subjects 12 to 62 days after the onset of AMI. *In situ* end-labeling of DNA fragmentation (TUNEL) and co-staining with caspase-3 were performed. Double-positive cells were defined as apoptotic and the apoptotic rate was calculated. Values are expressed as median and interquartile range. Co-stainings with muscle-actin, splicing factor (SC35), PCNA, *bax* and *bcl-2* were also performed. Apoptotic rates at site of infarction [25.4% (17.0–28.4%)] were significantly higher v those at remote regions [0.7% (0.5–0.8%); $P<0.001$] and significantly correlated to left ventricular longitudinal and transverse diameters [$r=+0.70$ ($P=0.016$) and $r=+0.63$ ($P=0.004$) respectively]. Moreover, in subjects with persistently occluded infarct-related artery (14 cases) there was a significantly higher apoptotic rate at the site of infarction compared to those (2 cases) with patent artery [26.0% (21.9–28.5%) v 4.5% (0.6% and 8,4%);$P=0.033$]. A significantly greater *bax* immuno-reactivity close to the infarction v remote areas was found ($P<0.001$). High grade apoptosis is present at sites of infarction in the later phases post AMI. This is more evident if the infarct-related artery is persistently occluded and signs of ventricular remodeling are present. These data may provide an explanation of progressive late left ventricular dysfunction.
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Key Words: Apoptosis; Myocardial infarction; Remodeling; Caspase-3; *bax*; *bcl2*.

Introduction

Apoptosis, or programmed cell death, is an energy-requiring and highly regulated process involved in development, homeostasis and senescence. Apoptosis is triggered by the activation of intracellular signalling pathways associated with the condensation of chromatin into crescentic caps of nuclear DNA at the periphery. Apoptotic cells then undergo extracellular degeneration or phagocytosis by macrophages without eliciting an inflammatory reaction.[1] It is acknowledged that apoptosis contributes both to homeostasis and human diseases. As such, it has been recognized as a key process in the adaptations of the cardiovascular system to its continuously changing demands.[2,3] Recently, it has been implicated as a fundamental pathogenetic mechanism in a variety of diseases including acute myocardial infarction (AMI), and post-ischemic and idiopathic dilated cardiopathy.[4–10] New techniques,

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